AD_____

Award Number: W81XWH-12-1-0510

TITLE: Prevention of Stimulant-Induced Euphoria with an Opioid Receptor Antagonist

PRINCIPAL INVESTIGATOR: *Thomas Spencer, M.D.*

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, MA 02114

REPORT DATE: October 2014

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
October 2014	Annual	30 September 2013- 29 September 2014

4. TITLE AND SUBTITLE
Prevention of Stimulant-Induced Euphoria with an Opioid Receptor Antagonist

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-12-1-0510

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Dr. Thomas Spencer

Email: Tspencer@partners.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Massachusetts General Hospital
Boston, MA 02114

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The protocol, sponsored by the Department of Defense, is a 6-week study examining whether Methylphenidate-induced euphoria can be attenuated by co-administration with Naltrexone In medication native young adults (age 18-30) with a euphoric response to MPH administered on the "Drug Feeling visit." In this double bind study, subjects will receive MPH and Naltrexone or a placebo to treat their ADHD symptoms over the course of the 6-week trial

15. SUBJECT TERMS- nothing listed

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	27	**19b. TELEPHONE NUMBER** *(include area code)*

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Table of Contents

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Section I: Introduction

The protocol, sponsored by the Department of Defense, is a 6-week study examining whether methylphenidate-induced euphoria can be attenuated by co-administration with naltrexone in medication naïve young adults (age 18-30) who exhibit a euphoric response to methylphenidate. In this double-blind study, subjects will receive methylphenidate and naltrexone or a placebo to treat their ADHD symptoms over the course of the 6-week trial.

Section II: Body

Currently, we are actively recruiting and enrolling subjects. The first subject was enrolled on January 24th, 2013, followed by a 2-month (no cost) break from the project to allow for Dr. Spencer's full recovery from his emergency coronary bypass surgery. Since the previous period of performance, study enrollment has continued to be ahead of schedule. Currently, 54 subjects have been initially screened and signed informed consent, compared to 19 subjects in the previous performance period. For each subject, clinicians performed a psychiatric evaluation and physical exam, as well as reviewed inclusion and exclusion criteria. The current enrollment report can be found at the end of this report in Table A.

Following informed consent and an initial interview with a study physician, research assistants conducted structured interviews (SCID/KSAD) and assisted the research coordinator in obtaining vital signs, a urine pregnancy and drug test, and administration of an electrocardiogram. Currently, 46 subjects have completed these further screening procedures, compared to 13 subjects in the previous performance period.

After these screening and evaluation procedures, subjects completed the baseline Drug Feeling Visit to determine if they experienced stimulant-induced euphoria. While we initially expected only 38% of participants to experience the desired likeability response (≥5 on the Drug Rating Questionnaire DRQ-S), currently 30 out of 36 subjects that have participated in this visit, or 83.33%, have fulfilled this portion of the inclusion criteria. The previous period of performance reported 9 subjects that experienced the stimulant-induced euphoria.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Upon completing the baseline Drug Feeling Visit, participants moved on to the randomized clinical trail for treatment with long acting methylphenidate (Ritalin LA) and double blind naltrexone. For this part of the study, participants came in for weekly visits with a study physician to monitor their response to the medication, changes in their ADHD symptoms, and any adverse events that arise. Medication was adjusted per the physicians' discretion and, depending on the response of the subject, may be titrated up to a maximum daily dose of 1.3mg/Kg/day. At the weekly visits, clinicians completed the AISRS and the CGI-ADHD to assess the subjects' ADHD symptoms and improvement.

On the week 3 and week 6 visits, subjects repeat the protocol from the Drug Feeling Visit with double-blind doses of instant release methylphenidate (IR MPH) instead of single blind. While the rating scales used following single blind IR MPH to determine subject eligibility at the baseline Drug Feeling Visit, the same rating scales used during the Week 3 and Week 6 Drug Feeling Visits are used as outcome measures. Currently, 21 subjects have completed the Week 3 Drug Feeling Visit, which is the midpoint of the study and the point at which their data is useful for analysis. The previous performance period reported 5 subjects to have completed this visit. Moreover, as this trial aims to collect data from 30 subjects, we have completed two-thirds of this data collection goal. Finally, 18 subjects have completed the entire study, compared to 2 subjects in the previous performance period.

The remaining subjects were terminated for various reasons. Eleven subjects were found ineligible after they were consented, which were either due to cardiovascular concerns about using stimulant treatment, a positive urine drug screen or failure to experience stimulant induced euphoria on the baseline Drug Feeling Visit. Eleven subjects have been dropped from the study, due to being lost to follow-up, the demanding time commitment, or plans of moving out of the area. Four subjects have been terminated from the study due to adverse events. Of those terminated due to adverse events, one developed negative mood side effects, most likely attributed to the study medication, and was subsequently terminated from the study and transitioned to clinical care for her ADHD treatment and to monitor her mood. Another subject

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

was terminated after he developed enlarged lymph nodes throughout his abdominal cavity, which was later identified as cancer. Study staff notified the Partners Healthcare IRB of this event, which confirmed the clinical assessment that this event was unrelated to study medication. The third subject experienced a reoccurrence of her peptic stress ulcers, and was thus terminated from the study and triaged to clinical care for her ADHD treatment. Lastly, one subject experienced substantial nausea and vomiting after taking the medication, and was therefore transitioned to clinical care for continued treatment of her ADHD symptoms.

In addition, various administrative changes have occurred since the previous performance period. On July 7th, Anna Hall was hired as the new Clinical Research Coordinator for this project, to replace the previous Clinical Research Coordinator, Ariana Koster, who had completed her time in the position. Ms. Hall has received extensive training in recruitment procedures, subject screening, scheduling, and has been trained by the previous research coordinator and Principal Investigator to acquire in-depth knowledge of the details of the study protocol. All study staff, including Ms. Hall, have undergone 'Good Clinical Practice and Human Subjects Protection' training prior to involvement in the study. All study staff have also completed or updated their CITI (Collaborative Institutional Training Initiative) training and passed the CITI certification exam, deeming them CITI certified. Ms. Hall has also been trained in taking vital signs and transferring specimens to the Massachusetts General Hospital CORE laboratory. She is currently being trained in conducting electrocardiograms and blood draws. Any procedures in which the study coordinator is not fully trained or needs assistance are conducted by other fully trained research assistants on study staff. Finally, the study's Grants Officer, Samar Nader, is currently on maternity. The interim Grants Officer is Christopher Decelles.

Several administrative amendments have also moved the study forward since the previous performance period. On October 15th, 2013, the Partners Healthcare IRB accepted an amendment to allow screening to occur over multiple visits, therefore allowing more flexibility for subjects' schedules. On December 2nd, 2013, the IRB approved an amendment to the

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

protocol, which allows for additional urine drug screens to be completed up to every visit based on clinician assessment of the subject's drug use history and concern of the subject using drugs after the initial screen. Lastly, on January 17th, 2014, the IRB approved an amendment to allow subjects to complete certain study visits by telephone when necessary. All of these amendments support smoother progress of the study. Please refer to the Appendix for documentation of all study amendments.

Furthermore, on April 24th, 2014, the IRB approved the Continuing Review for the study. The 2014 Continuing Review was then submitted along with all supplemental materials to the USAMRAA Human Research Protection Office for review on May 5th, 2014. Following minor clarifications, on May 27th we received notification that the US Army Medical Research and Material Command (USAMRMC), Office of Research Protections (ORP), and Human Research Protection Office (HRPO) found the protocol to be in compliance with Federal, DoD, and US Army human subjects protections requirements and approved continuation of the protocol through April 24th, 2015.

Section III: Key Research Accomplishments

- On October 15th, 2013, the IRB accepted an amendment to allow screening to occur over multiple visits.
- On December 2nd, 2013, the IRB approved an amendment to allow for additional urine drug screens to be completed up to every visit based on clinician assessment.
- On January 17th, 2014, the IRB approved an amendment to allow subjects to complete certain study visits by telephone.
- On April 24th, 2014, the Partners IRB approved the Continuing Review for the study.
- On May 27th, 2014, USAMRMC Office of Research Protections found the protocol to fully comply with DoD US Army and USAMRMC human subjects protection requirements and approved continuation of the protocol through April 24th, 2015.
- The Principal Investigator has trained new research staff in the specifics of the protocol.
- In July 2014, Anna Hall was hired and trained as the Clinical Research Coordinator for the study.
- All study staff have been CITI (Collaborative Institutional Training Initiative) certified.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

- 54 subjects have been consented and enrolled.
- 46 subjects have completed all screening procedures.
- 36 subjects have participated in the baseline Drug Feeling Visit, 30 of which experienced stimulant-induced euphoria.
- 21 subjects have completed the Week 3 Drug Feeling Visit, out of a goal of 30 subjects.
- 18 subjects have completed the entire study.

Section IV: Reportable Outcomes

To date, there are no reportable outcomes resulting from this research, as the medication blind will not be broken until the end of the study to ensure the integrity of the outcome measures.

Section V: Conclusion

While stimulant medicines are documented effective treatments of ADHD across the lifecycle, persistent concerns remain about their abuse potential that greatly inhibit their therapeutic use in clinical practice. Unfortunately, untreated ADHD is associated with high levels of impairment and disability that can profoundly adversely impact the lives of those affected during and after their military service. These include difficulties performing complex and demanding cognitive tasks under time constraints as required in the military, deficits in impulsivity, distractibility and emotional regulation that could endanger the life of the affected soldier and his or her peers, deficits in the interactions with peers and superiors, emotional impulsivity that could lead to low self esteem, substance abuse, criminality and accidents [1].

ADHD also affects veterans. Upon returning to civilian life, military personnel face many hurdles in redefining their role in society and securing employment. ADHD can certainly affect the ability to negotiate this transition. One stark example of this very issue is a study of homeless veterans that found that the majority (50/80) had ADHD [2]. Thus, the safe and effective treatment of ADHD is of great importance for military personnel after active service.

In addition to causing serious problems for enlisted personnel and veterans, ADHD is also a serious problem for military families. Since ADHD is estimated to afflict up to 10% of

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

children, a sizable number of servicemen's children may be afflicted with ADHD and suffer from its adverse impacts on the family and school. Such concerns may distract the enlisted man and interfere with the soldier's ability to perform his or her duties effectively during their absence from home. Thus, safe and effective treatment for ADHD can have a substantial, direct benefit to the families of servicemen and the piece of mind of the enlisted soldier.

Stimulants have long been used by the military for non-ADHD indications in the context of sleep loss and stress to diminish fatigue and motion sickness [3] as well as enhance alertness of pilots during lengthy flight [4, 5] as well as to enhance the abilities, marksmanship, cognitive performance and mood of soldiers [6-8].

Yet, despite their clear and unequivocal benefits, stimulants can also be abused. For example, in a study of almost 20,000 army inductees, 12 % (2,369) reported that they had used amphetamines prior to enlistment. This number represented 38% of all cases of drug use [9]. Further surveys indicate that 10 % of military personnel abuse stimulants during active duty [10] and there is increasing concern that stimulant misuse is often from diverted prescriptions. The concern about abuse potential of stimulants is compounded by the fact that ADHD is a known risk factor for drug and alcohol abuse and dependence [11]. Hence a safe stimulant formulation free of abuse potential would allow for effective treatment of ADHD for active military personnel, their children as well as veterans without concerns about misuse, abuse and diversion.

In addition to other researchers, we have documented that stimulants mediate abuse through their effects on brain opioid receptors [12]. This insight allowed us to posit a novel pharmacological approach to help mitigate the emergence of stimulant-associated abuse through blocking opiate receptors with Naltrexone, an opiate receptor antagonist. Thus, our study could lead to the development of an abuse-free stimulant that could provide the first effective and non-addictive stimulant treatment for ADHD. Such a treatment could have profound benefits to enlisted soldiers, veterans and their families, their treating physicians, and the military at large.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Section VI: References

1. Weiss, G. and L. Hechtman, *Hyperactive children grown up*, in *ADHD in children, adolescents, and adults*. 1993, Guilford Press: New York, NY.
2. Lomas, B. and P.S. Gartside, *Attention-deficit hyperactivity disorder among homeless veterans.* Psychiatr Serv, 1997. **48**(10): p. 1331-3.
3. Hoyt, R.E., et al., *Modafinil as a potential motion sickness countermeasure.* Aviat Space Environ Med, 2009. **80**(8): p. 709-15.
4. Gore, R.K., T.S. Webb, and E.D. Hermes, *Fatigue and stimulant use in military fighter aircrew during combat operations.* Aviat Space Environ Med. **81**(8): p. 719-27.
5. Caldwell, J.A. and J.L. Caldwell, *Fatigue in military aviation: an overview of US military-approved pharmacological countermeasures.* Aviat Space Environ Med, 2005. **76**(7 Suppl): p. C39-51.
6. Caldwell, J.A., et al., *Modafinil's effects on simulator performance and mood in pilots during 37 h without sleep.* Aviat Space Environ Med, 2004. **75**(9): p. 777-84.
7. McLellan, T.M., et al., *Caffeine maintains vigilance and marksmanship in simulated urban operations with sleep deprivation.* Aviat Space Environ Med, 2005. **76**(1): p. 39-45.
8. Westcott, K.J., *Modafinil, sleep deprivation, and cognitive function in military and medical settings.* Mil Med, 2005. **170**(4): p. 333-5.
9. Callan, J.P. and C.D. Patterson, *Patterns of drug abuse among military inductees.* Am J Psychiatry, 1973. **130**(3): p. 260-4.
10. Black, S., K.L. Owens, and R.P. Wolff, *Patterns of drug use: a study of 5,482 subjects.* Am J Psychiatry, 1970. **127**(4): p. 420-3.
11. Wilens, T.E., et al., *Does ADHD Predict Substance-Use Disorders? A 10-Year Follow-up Study of Young Adults With ADHD.* J Am Acad Child Adolesc Psychiatry. **50**(6): p. 543-53.
12. Zhu, J., et al., *Methylphenidate and mu opioid receptor interactions: A pharmacological target for prevention of stimulant abuse.* Neuropharmacology, 2011. **61**(1-2): p. 283-92.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Section VII: Appendices

Documentation of all Study Amendments through September 2014

AME 1 IRB Approval: 8/29/12

Approves revised Consent Form (1):
1. Changing study coordinator contact information;
2. Correcting minor formatting inconsistencies;
3. Clarifying that subjects will be taking Naltrexone (or placebo) once daily for the entire study, but will be taking SODAS-MPH twice daily for the entire study;
4. Removing reference to "study diaries" as subjects will not complete diaries as part of this trial.

AME 2 IRB Approval: 9/28/12

Added: Ariana Koster as a Research Coordinator/Mgr

AME 3 IRB Approval: 11/2/12

Approves revised Protocol Summary and Detailed Protocol decreasing the dose of naltrexone to 25 mg daily if the 50 mg dose is not well tolerated.

AME 4 IRB Approval: 11/15/13

Added: Jefferson Prince MD as a Co-Investigator. Removed: Anela Bolfek MD

AME 5 IRB Approval: 11/28/12

Approves revised Detailed Protocol (dated 06/15/2012) and Consent Form (1):
1. Changing the IR-MPH dosing to single-blind on the first likability assessment day (pre-baseline) only. The IR-MPH dosing will remain double-blind at the week 3 and week 6 likability assessments;
2. Adding handout "Likability Assessment Day Instructions;"
3. Executing the clinical blood labs on the first likability assessment day instead of at the initial visit.

AME 6 IRB Approval: 12/7/12

Notification that the Certificate of Confidentiality CC-MH-12-184 (dated 10/23/2012) has been approved by the NIMH.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

AME 7 IRB Approval: 12/29/12

1) Increase of age range for eligible participants from 18-24 to 18-30.
2) Subjects will be seen at a Massachusetts General Hospital outpatient site located at 55 Fruit St. WRN 705. Boston, MA 02114, instead of at 185 Alewife Brook Pkwy, Suite 2000. Cambridge, MA 02139.
-A revised Detailed Protocol, Protocol Summary (Version Date: 12/04/2012), and one Informed Consent (Version Date: 12/04/2012) reflect the changes made.

AME 8 IRB Approval: 1/2/13

Added: Andrea Spencer MD & Mai Uchida MD as Co-Investigators.

AME 9 IRB Approval: 2/5/13

Approves use of "Addiction Research Center Inventory -- Subject" form to be completed by the participant after completing the DQRS.

AME 10 IRB Approval: 2/4/13

Added: Emma Issenberg as a Reg. Coordinator/mgr. Removed: Paul Hammerness MD

AME 11 IRB Approval: 3/20/13

Added: Christopher Keary as a Co-Investigator

AME 12 IRB Approval: 3/14/13

Updated the Consent Form with the Principal Investigator's current contact phone number and reworks the description of the office location to improve clarity (p.2).

AME 13 IRB Approval: 7/16/13

Added: Rebecca Grossman as a Research Assistant.

AME 14 IRB Approval: 8/13/13

Approves posting for the MGH Clinical Trials Website and Broadcast emails, images and text for Facebook advertising, and a Facebook Ad Landing Page (the internet webpage that will open if potential subject clicks on the Facebook advertisement).

AME 15 IRB Approval: 9/19/13

Added: Olivia Bogucki, Stephannie Furtak, Brittany Hughes, Tara Kenworthy, Amanda Pope, and Courtney Zulauf as research assistants.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Removed: Emma Issenberg and Katie McDermott from study staff.

AME 16 IRB Approval: 10/15/13

1. Approves the option of breaking up the first screening visit so that it can be completed over the course of several days
2. Updates protocol documents to accurately reflect that Joseph Gonzalez-Heydrich, M.D. is the DSMB chair, not Marlene Freeman, M.D.
3. Corrects an error on the Consent Form that states that subjects will know whether they are receiving IR-methylphenidate or placebo on the Drug Feeling Visit. Subjects will not know whether they receive the active drug or placebo
4. Updates the length of the Drug Feeling Visit indicated on the Consent Form from 8 hours to 10-11 hours
5. Removes the text on the Consent Form stating that the Drug Feeling Day will take place within a month of the first Screening Visit
6. Updates study documents to include contact information for Dr. Andrea Spencer, an additional study clinician.

AME 17 IRB Approval: 12/2/13

Approves the addition of urine drug screens based on clinician assessment of the subject's drug use history and concerns of the subject using drugs after the initial screen. These additional urine drug screens may be conducted as frequently as each study visit and, like the baseline urine drug screen, will be confidential, labeled only with coded identifiers, and will be kept separate from the subject's medical record.

AME 18 IRB Approval: 1/17/14

Approves revised Protocol Summary and Detailed Protocol allowing subjects to complete visits 4, 5, 7, and 8 by phone and subjects may not complete two consecutive visits by phone. Consistent with office visits, all rating scales and assessments will be complete by a licensed psychiatrist during study phone visits, with the exception of collecting vital signs.

AME 19 IRB Approval: 2/3/14

Approves revised Protocol Summary (dated 02/03/2014), Detailed Protocol (dated 02/03/2014), and Consent Form (dated 02/03/2014) updating the Demographic Interview to be collected using a new form.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

AME 20 IRB Approval: 3/12/14

Removes Jefferson Prince, M.D. from study staff.

AME 21 IRB Approval: 5/6/14

Adds Leah Feinberg to study staff as the Regulatory Coordinator/Manager.

AME 22 IRB Approval: 5/29/14

Adds Brittany Albright, M.D. to study staff as a Co-Investigator.

AME 23 IRB Approval: 6/22/14

Added Lauren Rhodewalt to study staff as a Research Assistant.

AME 24 IRB Approval: 7/14/14

Added Anna Hall to study staff as Clinical Research Coordinator.

AME 25 IRB Approval: 7/24/14

Updated funding information in EPIC, the new healthcare software.

AME 26 IRB Approval: 7/28/14

Added Jessica Abrams to study staff as a Research Assistant and removes Rebecca Grossman.

AME 27 IRB Approval: 7/31/14

Added Nicholas Carrellas, Kristina Conroy, Jacqueline Davis, Emily Grimsley, and Natalie Plascencia to study staff as Research Assistants. Also added Amy Yule MD to study staff as Co-Investigator.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

Section VIII: Supporting Data

Table A: Enrollment Report

Self-Reported Ethnicity and Gender of All Enrolled Subjects				
Ethnic Category	**Males**	**Females**	**Unknown**	**Total**
Hispanic or Latino	5	3	0	8**
Not Hispanic or Latino	18	28	0	46
Unknown (individuals not reporting ethnicity)	0	0	0	0
Totals of All Enrolled Subjects*	23	31	0	54*
***Ethnic and Racial Categories: These totals must agree.**				

Self-Reported Race and Gender of All Enrolled Subjects				
Racial Categories	**Males**	**Females**	**Unknown**	**Total**
American Indian/Alaska Native	0	0	0	0
Asian	2	1	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	3	3	0	6
White	15	25	0	40
More than one race	1	2	0	3
Unknown or not reported	2	0	0	2
Totals of All Enrolled Subjects*	23	31	0	54*
***Ethnic and Racial Categories: These totals must agree.**				

Self-Reported Race and Gender of All Enrolled Hispanic or Latino Subjects				
Racial Categories	**Males**	**Females**	**Unknown**	**Total**
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	1	0	0	1
White	2	2	0	4
More than one race	0	1	0	1
Unknown or not reported	2	0	0	2
Totals of Enrolled Hispanic or Latino Subjects**	5	3	0	8**
****Hispanic or Latino Ethnic and Hispanic or Latino Race Enrollment Reports: These totals must agree.**				

Ethnic and Racial Definitions for the Minimum Standard Categories Above	
Hispanic or Latino:	A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.
American Indian or Alaska Native:	A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian:	A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent.
Native Hawaiian or Other Pacific Islander:	A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
Black or African American:	A person having origins in any of the black racial groups of Africa.
White:	A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

Table B: Adverse Events Log

Master Adverse Events Log: Prevention of Stimulant Induced Euphoria with an Opioid Receptor Antagonist

Subject ID	Date of AE	Description	Severity	Expected?	Related?	Changes/ Corrective Action	Date Reported to IRB
1770701	7/16/13	Stomache discomfort due to food	Mild	Expected	Unrelated	None	N/A
1770401	7/29/13	Seasonal Allergies	Mild	Expected	Unrelated	Pharmacologic	N/A
1770901	7/29/13	Headache	Mild	Expected	Unrelated	Pharmacologic	N/A
1770401	8/3/13	Increased Energy	Mild	Expected	Probable	None	N/A
1770401	8/3/13	Agitated/Irritable	Mild	Expected	Probable	None	N/A
1770701	8/3/13	Mild Headache in afternoon	Mild	Expected	Possible	None	N/A
1770401	8/13/13	Mild Abdominal Discomfort	Mild	Expected	Probable	None	N/A
1770701	8/15/13	Trouble falling asleep	Mild	Expected	Possible	None	N/A
1770701	8/15/13	Cough-Bronchitis	Moderate	Unexpected	Unrelated	None	N/A
1770401	8/19/13	Headache	Moderate	Expected	Unrelated	None	N/A
1770501	8/19/13	Headache	Mild	Expected	Unrelated	Pharmacologic	N/A
1770701	8/23/13	Difficulty Falling Asleep	Mild	Expected	Probable	None	N/A
1770701	8/24/13	Delayed Sleep	Mild	Expected	Possible	None	N/A
1770401	8/29/13	Headache Pain 5/10	Moderate	Expected	Possible	None	N/A
1770701	8/29/13	Cheek Biting	Mild	Expected	Possible	Pharmacologic	N/A
1770701	9/5/13	Cheek Biting	Mild	Expected	Possible	None	N/A
1770401	9/6/13	Headache When sstopped coffee	Moderate	Expected	Possible	None	N/A
1770401	9/14/13	Decreased Energy. Hard to get up in AM	Moderate	Expected	Possible	None	N/A
1770601	9/17/13	Insomnia- Difficulty Falling Asleep	Severe	Expected	Definitely	Pharmacologic + Altered Dose/Changed schedule	N/A
1770601	9/17/13	Early Waking	Mild	Expected	Possible	None	N/A
1770601	9/17/13	Less hungry than usual	Mild	Expected	Probable	None	N/A
1770601	9/17/13	Shakey Feeling	Moderate	Expected	Probable	Altered Dose/Changed Schedule	N/A
1770601	9/17/13	"Pressure"	Severe	Expected	Probable	Altered Dose/Changed Schedule	N/A
1770601	9/17/13	Just Nausea	Mild	Expected	Probable	None	N/A
1770601	9/17/13	Back Pain	Mild	Unexpected	Unrelated	None	N/A
1771001	9/17/13	More irritated than normal	Moderate	Expected	Possible	None	N/A
1771001	9/17/13	Decreased Appetite	Mild	Expected	Probable	None	N/A
1771001	9/17/13	Headache	Mild	Expected	Possible	Pharmacologic	N/A
1770601	9/23/13	Decreased Appetite	Mild	Expected	Possible	None	N/A

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Subject ID	Date of AE	Description	Severity	Expected?	Related?	Changes/ Corrective Action	Date Reported to IRB
1770601	9/23/13	Middle Insomnia (waking up before alarm	Mild	Expected	Possible	None	N/A
1770801	9/23/13	hospitalized for enlarged lymph nodes throughout the abdominal cavity	Severe	Unexpected	Unrelated	Terminated From Trial	9/23/13
1771001	9/24/13	Sad/Down	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1771001	9/24/13	anxious/worried	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1771001	9/24/13	Headache	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1770601	10/5/13	Increased Energy	Mild	Expected	Possible	None	N/A
1771001	10/11/13	Tense/Jittery	Moderate	Expected	Probable	Non-Pharmacological	N/A
1771001	10/11/13	Insomnia- Restless Sleep	Mild	Expected	Probable	None	N/A
1771001	10/18/13	Sad/Down	Moderate	Expected	Possible	None	N/A
1771001	10/18/13	Insomnia- Restless Sleep	Mild	Expected	Probable	None	N/A
1771001	10/18/13	Tense/Jittery	Moderate	Expected	Probable	None	N/A
1771001	10/18/13	Headache	Mild	Expected	Unrelated	Pharmacologic	N/A
1771001	10/18/13	Nausea	Mild	Expected	Unrelated	Pharmacologic	N/A
1771001	10/26/13	Insomnia- Restless Sleep	Moderate	Expected	Possible	Terminated From Trial	N/A
1771001	10/26/13	Sad/Down	Severe	Expected	Probable	Terminated From Trial	N/A
1771001	10/26/13	Nausea	Moderate	Expected	Probable	Terminated From Trial	N/A
1770601	10/27/13	Nausea	Moderate	Expected	Probable	None	N/A
1771401	10/27/13	Increased GI Activity	Mild	Expected	Probable	None	N/A
1771701	11/12/13	Takes 15 min to fall asleep	Mild	Expected	Probable	None	N/A
1771701	11/25/13	Nausea following sleep deprivation	Moderate	Expected	Probable	None	N/A
1771401	11/26/13	Heart beating fast on first day of meds. Tookd meds w/out food	Mild	Expected	Probable	None	N/A
1772701	12/7/13	Tingliness in extremities and pressure in head	Mild	Expected	Probable	None	N/A
1771401	12/13/13	Insomnia	Mild	Expected	Probable	None	N/A

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Subject ID	Date of AE	Description	Severity	Expected?	Related?	Changes/ Corrective Action	Date Reported to IRB
1772401	12/19/13	Mild nausea when took medication without food	Mild	Expected	Probable	None	N/A
1772201	12/20/13	Felt anxious several hours following Ritalin IR administration although improved within a few hours	Mild	Expected	Probable	None	N/A
1772501	12/20/13	Tense/Jittery feeling in chest	Moderate	Expected	Probable	None	N/A
1772501	12/20/13	Dry mouth	Mild	Expected	Probable	None	N/A
1772201	12/23/13	1 hr nausea (resolve on own)	Mild	Expected	Possible	None	N/A
1772701	12/23/13	Mild Nausea after taking PM dose	Mild	Expected	Probable	None	N/A
1772201	1/2/14	Anxious/Worried at night	Moderate	Expected	Probable	None	N/A
1772201	1/2/14	Nausea between doses	Mild	Expected	Probable	None	N/A
1772701	1/3/14	Nausea	Mild	Expected	Probable	None	N/A
1772701	1/3/14	Sad/Down	Moderate	Expected	Probable	None	N/A
1772501	1/21/14	Emotional Dreams	Mild	Expected	Unlikely	None	N/A
1772501	1/21/14	anxious/worried	Mild	Expected	Probable	None	N/A
1772101	1/25/14	Stomach Cramp/Upset stomache	Mild	Expected	Possible	None	N/A
1772201	1/25/14	anxious/worried in AM	Moderate	Expected	Probable	None	N/A
1772201	1/25/14	Insomnia	Moderate	Expected	Probable	None	N/A
1772501	1/25/14	Tense/Jittery when took meds without food	Moderate	Expected	Probable	None	N/A
1772701	1/25/14	Nausea	Moderate	Expected	Probable	None	N/A
1772701	1/25/14	Decreased Energy at end of day	Moderate	Expected	Probable	None	N/A
1773401	1/25/14	Tense/Jittery for a few hours	Mild	Expected	Probable	None	N/A
1772001	2/11/14	Going to bed a bit later	Mild	Expected	Definitely	None	N/A
1773101	2/11/14	Nausea	Mild	Expected	Probable	None	N/A
1773101	2/11/14	Decreased Energy	Mild	Expected	Probable	None	N/A
1773101	2/11/14	Agitated/Irritable	Mild	Expected	Probable	None	N/A
1773401	2/11/14	Slight indigestion feeling	Mild	Expected	Probable	None	N/A
1772001	2/18/14	Palpitations	Mild	Expected	Probable	Non-Pharmacological	N/A
1773401	2/19/14	Insomnia	Mild	Expected	Probable	None	N/A
1773101	2/25/14	"feeling warm"	Mild	Expected	Possible	None	N/A
1772001	3/8/14	pulse increase	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1772001	3/8/14	Insomnia	Mild	Expected	Possible	None	N/A
1773101	3/8/14	"feels hot"	Mild	Expected	Possible	None	N/A

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Subject ID	Date of AE	Description	Severity	Expected?	Related?	Changes/ Corrective Action	Date Reported to IRB
1773501	3/10/14	jitteriness x36hours	Moderate	Expected	Probable	None	N/A
1773501	3/10/14	Sweating at night	Moderate	Expected	Probable	None	N/A
1773501	3/10/14	Decreased Appetite	Mild	Expected	Probable	None	N/A
1773301	3/13/14	Dry mouth	Mild	Expected	Probable	None	N/A
1773501	3/18/14	Poor Appetite	Mild	Expected	Probable	Altered Dose/Changed Schedule	N/A
1773501	3/18/14	Pain from injured toe	Mild	Unexpected	Unrelated	None	N/A
1773501	3/18/14	Tense/Jittery	Mild	Expected	Probable	None	N/A
1773101	3/20/14	flushed at times	Mild	Expected	Probable	None	N/A
1773301	3/21/14	Nausea	Mild	Expected	Probable	None	N/A
1773301	3/21/14	Headache	Mild	Expected	Possible	None	N/A
1773301	3/29/14	dry mouth	Mild	Expected	Probable	Altered Dose/Changed Schedule	N/A
1773301	3/29/14	Headache	Moderate	Expected	Possible	Pharmacologic + Altered Dose/Changed schedule	N/A
1773301	3/29/14	Insomnia	Mild	Expected	Possible	None	N/A
1773301	4/4/14	Headache	Mild	Expected	Probable	Pharmacologic	N/A
1773501	4/10/14	"Crash" at end of day	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1773301	4/14/14	Palpitations	Mild	Expected	Probable	None	N/A
1774201	6/10/14	Nausea	Mild	Expected	Possible	None	N/A
1774701	6/10/14	eye twitch	Mild	Expected	Possible	None	N/A
1774701	6/10/14	insomnia	Mild	Expected	Probable	None	N/A
1774701	6/10/14	Headache	Mild	Expected	Possible	None	N/A
1774501	6/12/14	nausea/ vomiting	Moderate	Expected	Probable	Terminated From Trial	N/A
1774201	6/17/14	Tense/Jittery	Moderate	Expected	Possible	None	N/A
1774201	6/17/14	sedation	Moderate	Unexpected	Possible	None	N/A
1774201	6/17/14	Mentral Cramps	Moderate	Unexpected	Unrelated	Pharmacologic	N/A
1774701	7/3/14	Increased sweating	Moderate	Expected	Possible	None	N/A
1774701	7/3/14	Insomnia	Mild	Expected	Probable	None	N/A
1774701	7/17/14	Increased sweating	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1774801	7/29/14	Headache	Mild	Expected	Probable	Pharmacologic	N/A
1774801	7/29/14	Mucosal Dryness- dry mouth	Mild	Expected	Probable	None	N/A
1774801	8/7/14	Headache	Mild	Expected	Probable	None	N/A
1774801	8/7/14	Mucosal Dryness- dry mouth	Mild	Expected	Probable	None	N/A
1775201	8/19/14	Neurological- Numbness of right index finger	Mild	Unexpected	Unlikely	None	N/A

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

Subject ID	Date of AE	Description	Severity	Expected?	Related?	Changes/ Corrective Action	Date Reported to IRB
1774801	8/22/14	Mucosal Dryness-dry mouth	Mild	Expected	Probable	None	N/A
1775101	8/28/14	Nausea/Vomit/Diarr	Moderate	Unexpected	Unlikely	Non-Pharmacological	N/A
1775201	9/5/14	Decreased Appetite	Mild	Expected	Possible	None	N/A
1775201	9/5/14	Nausea	Mild	Expected	Possible	None	N/A
1775201	9/5/14	Headache	Mild	Expected	Possible	Pharmacologic	N/A
1774301	9/9/14	Depressed mood	Mild	Expected	Probable	None	N/A
1775201	9/12/14	Nausea	Mild	Expected	Possible	None	N/A
1775201	9/12/14	Decreased Appetite	Mild	Expected	Possible	None	N/A
1775401	9/19/14	Mucosal Dryness-dry mouth	Mild	Expected	Probable	None	N/A
1774301	9/23/14	Headache-discomfort in temporal part of head	Moderate	Expected	Probable	Pharmacologic + Altered Dose/Changed schedule	N/A
1775201	9/27/14	Decreased Appetite	Moderate	Expected	Probable	Altered Dose/Changed Schedule	N/A

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Table C: Minor Deviations

Minor Deviations Tracking Log

Protocol deviations are any deviation from the IRB-approved protocol that are not approved prospectively by the IRB. **Major protocol deviations** are deviations from the IRB approved protocol that "has the potential to negatively impact subject safety, the integrity of study data or subject's willingness to participate in the study". **Minor protocol deviations** are deviations that do not have the potential to negatively impact subjects, their willingness to participate or data integrity. **Minor deviations include,** but are not limited to, protocol deviations such as out of window visits, missing tests/labs, missing original/signed consent form (copy exists), missing PI signature on consent form(s), use of expired/outdated consent form that includes all relevant information, over-enrollment, failure to submit continuing review prior to expiration of IRB approval.

Instructions: This log is to be used for tracking and reporting minor deviations according to Reporting Unapproved Deviations in PHRC-Approved Research policy: http://healthcare.partners.org/phsirb/Guidance/Reporting_Unapproved_Deviations_in_PHRC-Approved_Research.1.11.pdf. Minor deviations are to be reported **ONLY** at continuing review. **NOTE: Entries in the log must be typed**.

PI:	Thomas Spencer, M.D.
Protocol #	2012-P-000918
Title:	Prevention of stimulant Induced Euphoria with an Opioid Receptor Antagonist
Sponsor:	Department of Defense

Date Deviation Discovered	Date Deviation Occurred	Subject Study ID	Description of Deviation	Description of Corrective Action	Date Sponsor Notified	Date Sponsor Approved	Recorded by / Date
6/14/13	6/14/13	1770201	The blood draw was not completed on Drug Feeling visit after 2 different phlebotomy-trained RAs attempted to locate the subject's veins but were unable to.	Under instruction of the PI, we will continue without 1770201's blood sample. A note to file was prepared to explain this. While safety labs are usually completed at this visit, 1770201 did not meet criteria at the Drug Feeling Visit and therefore 1770201 will not be able to move to the randomized trial. Thus the safetly labs were not completed.	N/A	N/A	Ariana Koster 6/20/13
8/5/13	8/5/13	1770401	At the Drug Feeling Visit, subject 1770401 informed study staff last minute that he had to leave early and did not complete the final DRQS and ARCI.	Under direction of the PI, we will proceed without having the subject complete these rating scales. A note to file was prepared to explain the situation. The subject was reminded of the time commitment necessary to participate in the study.	N/A	N/A	Ariana Koster 8/5/14
8/24/13	8/24/13	1770401	The Blood draw was not completed on Drug Feeling visit after 2 different phlebotomy-trained RAs attempted to locate the subject's veins but were unable to	Under instruction of the PI, we will continue without 1770401's blood sample from this visit. A note to file was prepared to explain this. The missed blood draw did not include safety labs,	N/A	N/A	Ariana Koster 8/27/14
9/16/13	9/16/13	1770401	Subject 1770401refused to have his blood drawn for his week 6 visit as he did not want to have bruises on his arm.	Under instruction of the PI, will continue without 1770401 blood sample from this visit. The missed blood draw did not include safety labs.	N/A	N/A	Ariana Koster 9/17/13
9/17/13	7/16/13	1770701	Subject 1770701's screening procedures were completed over several visits.	This policy is consistent with other studies within the department and we have submitted an amendment to allow the screening procedures to be broken up over several days, going forward.	N/A	N/A	Ariana Koster 9/17/13
8/3/13	8/3/13	1770701	The Blood draw was not completed on Drug Feeling visit after 2 different phlebotomy-trained RAs attempted to locate the subject's veins but were unable to.	Under instruction of the PI, we will continue without 1770701's blood sample from this visit. 1770701 went to the MGH official lab to complete her safety labs for the visit after she was done with her study visit.A note to file was prepared to explain this.	N/A	N/A	Ariana Koster 9/17/13
9/17/13	8/2/13	1770601	Subject 1770601's screening procedures were completed over several visits.	This policy is consistent with other studies within the department and we have submitted an amendment to allow the screening procedures to be broken up over several days, going forward	N/A	N/A	Ariana Koster 9/17/13

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Date Deviation Discovered	Date Deviation Occurred	Subject Study ID	Description of Deviation	Description of Corrective Action	Date Sponsor Notified	Date Sponsor Approved	Recorded by / Date
8/24/13	8/24/13	1770401	Subject 1770401 informed study staff that he needed to leave his week 3/ Drug Feeling Visit early and therefore did not have a break between the morning and afternoon dosing, as approved by the PI	Study staff re-emphasized the importance of being present for the full study visits and asked 1770401 to confirm that he will be able to stay for the full study visits for the rest of the study.	N/A	N/A	Ariana Koster 9/17/13
10/2/01	10/2/13	1770501	Subject 1770501completed her 4th morning DQRS rating scale 37min late on her baseline Drug Feeling visit. 1770501did not notice the DQRS after completing the ARCI and study staff did not notice this oversight for 37 min.	The subject completed the rating scale as soon as the problem was noticed. Study staff were reminded to check to make sure all rating scales are completed at the appropriate times during the visit. A note to file was prepared to explain this.	N/A	N/A	Ariana Koster 10/5/13
10/3/13	10/3/13	1770501	Subject 1770501ate prior to arriving for her baseline Drug Feeling Visit	Study staff emphasized the importance of following the instructions for study visits. A note to file was prepared to document this	N/A	N/A	Ariana Koster 10/5/13
10/3/13	10/3/13	1770501	The Blood draw was not completed on Drug Feeling visit after 2 different phlebotomy-trained RAs attempted to locate the subject's veins but were unable to.	Under instruction of the PI, we will continue without 1770501 blood sample from this visit. 1770501 was instructed to go to the MGH official laboratory to complete her safety labs but was lost to follow up as study staff could not contact her after this visit. A note to file was prepared to document this.	N/A	N/A	Ariana Koster 10/5/13
10/5/13	10/5/13	1770601	Subject 1770601's week 3 visit was 12 days after her week 2 visit, outside of the 9-day visit window.	Study staff were reminded of the importance of scheduling study visits within 9 days of the last study visit. The subject was reminded to contact study staff with any study related problems between visits.	N/A	N/A	Ariana Koster 10/5/13
10/5/13	10/5/13	1770601	On Subject 1770601week 3 Drug Feeling Visit, the 2nd morning DQRS rating scale was not completed. 1770601 did not notice the DQRS after completing the first rating scale, and study staff did not realize that the rating scale was incomplete until it was time for the next rating scale.	Study staff were reminded to check to make sure all rating scales are completed at the appropriate times during the visit. A note to file was prepared to document this missing data.	N/A	N/A	Ariana Koster 10/5/13
10/25/13	10/25/13	1771001	Study clinician's CITI certification had expired when she completed a study visit.	The study clinician completed CITI re-certification on 10/27/2013. A note to file was prepared, and study staff were reminded of the importance of ensuring that all certifications are current.	N/A	N/A	Ariana Koster 10/25/13
10/25/13	10/25/13	1772001	Study clinician's CITI certification had expired when she completed a study visit.	The study clinician completed CITI re-certification on 10/27/2013. A note to file was prepared, and study staff were reminded of the importance of ensuring that all certifications are current.	N/A	N/A	Ariana Koster 10/25/13
10/25/13	6/14/13	1770201	The first and second screening visit were completed over a month apart	This policy is consistent with other studies within the department and we have submitted an amendment to allow this going forward.	N/A	N/A	Ariana Koster 10/25/13
10/25/13	10/2/13	1770301	The first and second screening visit were completed over a month apart	This policy is consistent with other studies within the department and we have submitted an amendment to allow this going forward.	N/A	N/A	Ariana Koster 10/25/13

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Date Deviation Discovered	Date Deviation Occurred	Subject Study ID	Description of Deviation	Description of Corrective Action	Date Sponsor Notified	Date Sponsor Approved	Recorded by / Date
10/25/13	10/2/13	1770501	The first and second screening visit were completed over a month apart	This policy is consistent with other studies within the department and we have submitted an amendment to allow this going forward.	N/A	N/A	Ariana Koster 10/25/13
10/27/13	10/27/13	1770601	Subject 1770601 did not complete a blood draw on her week 6 Drug Feeling Visit. Subject 1770601 became sick to her stomach the second hour after her morning dose. While subject 1770601 wanted to finish the study visit, she felt as though a blood draw would exacerbate her nausea and requested that we not draw her blood.	Since this blood draw is not essential for subject safety or the integrity of the study data, under the direction of the PI we will forgo the blood samples from this visit. A note to file was prepared to document this.	N/A	N/A	Ariana Koster 10/28/13
11/19/13	11/19/13	1770301	Subject 1770301's week 3 visit was 13 days after his week 2 visit, outside of the 9 day visit window.	Study staff were reminded of the importance of scheduling study visits within 9 days of the last study visit. The subject was reminded to contact study staff with any study related problems between visits.	N/A	N/A	Ariana koster 11/22/13
12/7/13	12/7/13	1772501	After subject Subject 1772501's screening visit, study staff 1772501 that her EKG had been incorrectly administered. We therefore readministered the EKG at the beginning of her Drug Feeling Visit, prior to administering the study drug.	The EKG was completed and signed off by a study physician prior to completing any Drug Feeling Visit tasks. Study staff was reminded to confirm that the EKG was properly administered before the end of the Screening visit visit. A note to file was prepared to document this.	N/A	N/A	Ariana Koster 12/11/13
12/12/13	12/12/13	1771201	At his first Drug Feeling Visit, subject 1771201 informed study staff last minute that he had to leave early and did not complete the final DRQS and ARCI.	As compliance during study visits has been a consistent problem for subject 1771201, study staff decided to terminate Subject 1771201 from the trial.	N/A	N/A	Ariana Koster 12/12/13
12/13/13	12/13/13	1771701	Subject 1771701's week 6 visit was 10 days after her week 5 visit, outside of the 9 day study window.	Study staff were reminded of the importance of scheduling study visits within 9 days of the last study visit. The subject was reminded to contact study staff with any study related problems between visits.	N/A	N/A	Ariana Koster 12/13/13
12/20/13	12/20/13	1772501	Subject 1772501was only able to complete part of her Cognitive Battery assessment during her week 0 visit as her visit with the clinician ran late and she had to leave for a previous engagement.	Subject 1772501 completed the rest of her Cognitive Battery assessment at her wk1 visit. Subject 1772501was reminded to budget sufficient time to complete all study tasks and to leave extra time in her schedule in case her visit runs late. A note to file was completed.	N/A	N/A	Ariana Koster 12/27/13
1/3/14	1/3/14	1772701	Subject 1772701's wk 2 visit occurred 11 days after his week 1 visit, outside the 9 day visit window.	Study staff were reminded of the importance of scheduling study visits within 9 days of the last study visit. The subject was reminded to contact study staff with any study related problems between visits.	N/A	N/A	Ariana Koster 1/3/14

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Date Deviation Discovered	Date Deviation Occurred	Subject Study ID	Description of Deviation	Description of Corrective Action	Date Sponsor Notified	Date Sponsor Approved	Recorded by / Date
1/25/14	1/25/14	1772501	While subjects are asked to fast until the 3rd hour of the Drug Feeling Visit, on subject 1772501's wk6 visit/Drug Feeling Visit she expressed concerns that she would experience the same discomfort due to dry mouth that she had experienced on the previous Drug Feeling Visit. In an effort to cause as little discomfort to the subject as possible, study staff provided her with a sucking candy to consume if she experienced dry mouth.	Under direction of the doctor on site, study staff continued with the Drug Feeling Visit as usual and a note to file was completed explaining the situation.	N/A	N/A	Ariana Koster 2/5/14
1/25/14	1/25/14	1773101	The Blood draw was not completed on Drug Feeling visit after 2 different phlebotomy-trained RAs attempted to locate the subject's veins but were unable to.	Under instruction of the PI, we will continue without Subject 1773101's blood sample from this visit. A note to file was prepared. Study staff accompanied Subject 1773101's to the central MGH phlebotomy lab to complete her safety labs.	N/A	N/A	Ariana Koster 2/5/14
2/20/14	2/14/14	1773501	During his Cognitive Battery assessment, subject 1773501did not complete the 1st page of WRAT math as his scrap paper was covering the missed page.	Under direction of the PI we will proceed without this portion of the assessment as all necessary information for inclusion in the study was already obtained. A note to file was completed to document this.	N/A	N/A	Ariana Koster 2/20/14
3/31/14	2/1/13	170201	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	7/12/13	1770301	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	7/15/13	1770401	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	8/7/13	1770501	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	7/24/13	1770601	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	7/29/13	1770701	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Date Deviation Discovered	Date Deviation Occurred	Subject Study ID	Description of Deviation	Description of Corrective Action	Date Sponsor Notified	Date Sponsor Approved	Recorded by / Date
3/31/14	7/30/13	1770801	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	8/8/13	1770901	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	8/13/13	1771001	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	8/22/13	1771101	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	10/3/13	1771201	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	10/18/13	1771401	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	9/30/13	1771601	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	9/26/13	1771701	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	10/15/13	1771801	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	10/18/13	1772001	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	10/24/13	1772101	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	11/11/13	1772201	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Date Deviation Discovered	Date Deviation Occurred	Subject Study ID	Description of Deviation	Description of Corrective Action	Date Sponsor Notified	Date Sponsor Approved	Recorded by / Date
3/31/14	11/14/13	1772301	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	11/15/13	1772401	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	12/12/13	1772501	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	11/20/13	1772601	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	12/2/13	1772701	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	1/10/14	1773101	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	1/9/14	1773201	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	1/31/14	1773301	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	1/23/14	1773401	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	2/14/14	1773501	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	2/4/14	1773601	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	3/12/14	1773701	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

Date Deviation Discovered	Date Deviation Occurred	Subject Study ID	Description of Deviation	Description of Corrective Action	Date Sponsor Notified	Date Sponsor Approved	Recorded by / Date
4/2/14	4/2/14	1773901	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	3/13/14	1774001	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
4/16/14	4/16/14	1774101	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
7/24/14	7/22/14	1774801	On 7/14/14, Olivia Bogucki was removed from study staff. On 7/22/14, the new coordinator was unable to complete vitals because she was not trained. Olivia Bogucki completed vitals without being on study staff.	All study staff have been reminded of the importance of following the approved protocol.	N/A	N/A	Anna Hall 07/24/14
7/24/14	7/23/14	1775001	On 7/14/14, Olivia Bogucki was removed from study staff. On 7/23/14, the new coordinator was unable to complete vitals because she was not trained. Olivia Bogucki completed vitals without being on study staff.	All study staff have been reminded of the importance of following the approved protocol.	N/A	N/A	Anna Hall 07/24/14
7/25/14	7/15/14	1775101	A physical exam was not conducted during Subject 1775101's Week 99 visit on 07/15/14. A physician will conduct the physical exam before administering any medication on the subject's baseline Liking Day visit. There is no impact on subject safety	All study staff have been reminded of the importance of being mindful that all planned assessments be conducted at the appropriate visit.	N/A	N/A	Anna Hall 07/29/14